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REVIEW ARTICLE

Breast Cancer Vaccine – Prioritizing Deterrence

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ABSTRACT

The control of the immune system through the administration of avaccine to direct a successful and enduring immune response against breast cancer cells is an alluring method. Vaccine would have a few hypothetical preferences over standard therapy, including low toxicities, high specificity, and long lasting efficacy because of the establishment of immunological memory. On the other hand, Breast Cancer vaccines have failed to exhibit significant results in clinical trials as such. This reflects the inborn trouble in breaking the complex immune escaping mechanism created by tumor cells. New vaccine ought to have the capacity to evoke complex immunologic reaction including numerous immune effectors, for example, Cytotoxic and antibody secreting B cells, innate immunity effectors, and memory cells. In addition, particularly in patients with large tumor burdens and metastatic disease, combining vaccines with different procedures, for example, systemic Breast cancer treatments, passive immunotherapy, or immunomodulatory agents could expand the viability of each methodology.

Breast Cancer is immunogenic and there are a few tumor related antigens for which breast cancer vaccine have been produced. Breast cancer vaccine is intended to stimulate the immune response at different steps in the local antigen processing pathway for immune surveillance. Human epidermal growth factor receptor 2 (HER-2/neu), mucin 1 (MUC-1), and human telomerase reverse transcriptase (hTERT) are probably the most investigated antigens effectively being focused for vaccination in breast cancer patients.

Key-word: Breast Cancer, MUC-1, hTERT, HER-2/neu, USFDA, IHC, DCs, TAAs

INTRODUCTION

In spite of advances in adjuvant treatment, a significant proportion of women diagnosed with early breast cancer will eventually relapse with metastatic disease. Moreover, 4% to 10% of women will give metastatic disease at the time of initial diagnosis[1]. The management of metastatic Breastcancer (MBC) is focused around various tumor-related characteristics including anatomical sites of ailment, hormonal sensitivity of the tumor, and Her2 status and may incorporate hormonal, cytotoxic and molecularly focused treatments. Albeit randomized correlations of cytotoxic chemotherapy versus observation are lacking, survival advantage can be construed from a mixture of studies which contrast a more viable and a less successful regimen[2-3]. Case in point, general survival advantages have been exhibited for Docetaxel and capecitabine versus capecitabine alone in anthracycline pretreated patients and for gemcitabine and paclitaxel versus paclitaxel alone as first-line therapy.

Recently, advances in early detection and more viable medications have decreased the mortality rate. In spite of this advancement, Breast Cancer remains a main reason for death in the female population globally[4]. In this situation, controlling the immune framework to direct a powerful and long haul immune reaction against Breast Cancer cells through the administration of avaccine is an appealing strategy. Tumor vaccine would have a few hypothetical favorable circumstances over standard therapies. First and foremost, the perfect tumor vaccine would induce strong and durableimmune reaction against abroad range of tumor antigens. It could be effectively administered and manufactured, with unobtrusive symptoms run of the mill of conventional chemotherapies. Also, it would avert further tumor recurrences[5], because of the foundation of tenacious immune memory. At present, nonetheless, active immunotherapeutic strategies against cancer have neglected to satisfy the above desires results in clinical trials. This reflects the characteristic trouble in discovering ideal targets for a cancer vaccination, route of administration and the most immunologically favorable setting of infection (e.g., low tumor load, not intensely pretreated patients). Above all, it reflects the trouble in

breaking the complex immune escaping mechanism created by cancer cells[6].

Breast cancer antigens

The pledge of tumor vaccine lies in the dazzlingly targeted nature, negligible known adverse events and potential for enduring immunologic memory, which can potentially annihilate cancer at a reserved time from vaccination. Despite these potential advantages, there are no commercial Breast cancer vaccines endorsed in the USFDA, regardless of more than seventy pharmaceuticals organizations and various research labs involved in breast cancer vaccine development[7-9]. HER-2/neu, MUC-1, and hTERT are probably the most contemplated antigens effectively being focused for vaccination in breast cancer patients and there are various recent clinical trials showing empowering progress throughout the last several years.

The HER-2/neu protein is a part of the epidermal growth factor receptor family. During adult life, the HER-2/neu protein is weakly perceptible in the epithelial cells of most ordinary tissue, however is expressed fundamentally amid human fetal development[10]. Alterations in the structure, copy number, or expression of epidermal growth factor receptor genes assume a part in the pathogenesis in an assortment of human malignancies, including breast cancer. Over expression by immunohistocytochemistry (IHC) and amplification of gene by fluorescent in situ hybridization (FISH) has been recognized in numerous cancer, for example, Breast, ovarian, and gastric[11]. In Breast cancer, HER-2/neu amplification was connected with a more awful prognosis preceding the development of HER-2/neu controlled treatment with trastuzumab. The HER-2/neu oncogenic protein is likewise a tumor antigen. HER-2/neu has been discovered to be a magnificent target for immunotherapy, including monoclonal therapy which has exhibited clinical profit in both the adjuvant and metastatic situation.

MUC-1 (episialin, epithelial membrane antigen, Ca15-3 antigen) is an exceedingly O-glycosylated mucin-like transmembrane glycoprotein encoded on chromosome 1. In most typical glandular epithelia cells, MUC-1 is expressed on the apical surface. Over expression of an under glycosylated manifestation of MUC-1 happens in about all breast carcinomas[12-14]. In a latest study, irregular MUC-1 expression was seen in roughly 93% of 237 cases. The prognostic importance of MUC-1 overexpression is indistinct, with studies reporting better, no bearing, and more terrible prognosis in overexpressing patients. Utilizing another monoclonal antibody steered at the protein spine, and subsequently not subject to glycosylation, diverse film staining examples were assessed. MUC-1 staining specimens were connected with relapse free survival (RFS) and OS and exhibited that apical and diffuse cytoplasmic specimens anticipated better RFS and OS, while whole film, focal cytoplasmic and inside out patterns had no critical relationship with RFS and OS. In spite of the fact that not dependably prognostic, the unusual expression of MUC-1 in 93% of breast cancers yields a very nearly general target for immunotherapy in breastcancer patients. Significantly, a patient with an anti MUC-1 immune reaction to her malignancy at diagnosis, whether this reaction is a cellular reaction or antibody interceded, may live more than a patient without an immune reaction to her cancer[15].

Telomerase is a ribonucleoprotein complex that keeps up chromosomal integrity by securing telomeric DNA for constant cell multiplication. The complex contains telomerase reverse transcriptase (TERT) and a ribonucleic acid (RNA) template[16-18]. hTERT is a large protein of 1132 amino acid residue that has wide articulation in more than 85% of all human cancer, with practically zero interpretation in ordinary somatic cells. Peptides of hTERT degradation are displayed on the tumor cell surface as antigens by the MHC class I and II pathways. Patients abating from their threat regularly have large amounts of CD8+ receptive T cells towards hTERT peptide I540, though patients with active disease frequently have lower levels of reactive T cells. Given that hTERT is differentially expressed in cancer with almost no expression in somatic cells, that its hindrance in invitro prompts growth arrest, and that it seems to assume a vital role in carcinogenesis, this antigen is a potential therapeutic focus for a few malignancies, including Breast cancer[19].

Albeit numerous proteins have been shown to be immunogenic in breast cancer, HER-2/neu, MUC-1, and hTERT are effectively being contemplated as antibody immunogens in human clinical trials. Also, a mixed bag of vaccineconstructs have been created to focus on these antigens, in this way giving cases of the distinctive methodologies accessible for immunizing against Breast cancer[20].

Targets and approaches of Breast Cancer vaccines

It has been confirmed that the immune system assumes a part in controlling tumor development, and adaptive immunity is the primary mediator of "spontaneous" relapse of specific types of cancers. The immune system

can perceive a few types of antigens expressed on tumor cell surfaces, specifically the tumor-associated antigens (TAAs)[21-23].

TAAs are found in immune system effectors, for example, T-cells by the tumor itself, through the major histocompatibility complex (MHC) or, more probable, by antigen presenting cells (APCs), specifically macrophages and dendritic cells (DCs)[24]. These cells are vital in handling antigens into immunogenic peptides and introducing them to T-cells through the MHC complex. Through an intricate and regulated system of co-activator and inhibitory molecules expressed on the cell surface, these cells assume a vital part in preparing T lymphocytes and enacting an immunogenic reaction against particular targets. The vicinity of tumor- invading lymphocytes has been related with better visualization in a few sorts of cancers. However, tumor cells frequently develop the ability to bypass the surveillance of the immune system. In the tumor microenvironment, molecules, for example, VEGF, TGF-β, and interleukins are abundant and both effectively down regulate the immune function and advance tumor progression, attack, and metastasis[25-27].

Activation of the immune system could be upgraded by including adjuvant compounds, and appropriate monitoring techniques ought to be incited to evaluate the immunologic response. Recently, new techniques, for example, the utilization of nanoparticles and liposome formulations, which may enhance efficacy of vaccines, and preclinical studies with intriguing results have been published[28]. Indeed, different vaccine formulation have been tried in this way, yet none of these was demonstrated to be superior in all circumstances.

Peptide-based vaccination

Peptide-based vaccine work by activatingimmune reactions (counting antibodies, cytotoxic T lymphocytes [CTLs], and helper T-cells) utilizing antigenic epitopes derived from TAAs .Many of the first cancervaccine methodologies concentrated on instigating tumor-particular CD8+ cells with MHC class I restricted short peptides. It is presently clear that these CD8+ T-cell reactions are commonly weak and short-lived. Further investigations have elucidated that triggering the CD4+ T-cell reaction is discriminating for augmenting tumor resistance, as it both enhances the CD8+ T-cell reaction and supports the humoral antitumor immune response[29-30]. Thus, researchers have concentrated on investigating peptide-based vaccines that have the capacityto triggerboth CD4+ and CD8+ reactions, utilizing longer peptides and mixtures of epitopes.

Peptide vaccines have a few potential preferences, which incorporate simple assembling, effortlessly evaluate immunological reaction, and low expected toxicities. These points of interest have made the peptide-based vaccination generally contemplated and utilized in clinical trials. Nonetheless, this strategy shows some target limits. Firstly, to be compelling, peptide vaccines regularly require co-administration of an immunological adjuvant. Adjuvants assume a vital role in favoring enrollment and effective incitement of immune effectors. Identification of a significantly more effective adjuvant for a given vaccine is important for the effectiveness of the formulation and has been the object of serious exploration[31]. Secondly, the majority of the peptide-based vaccines tried are confined to HLA-A2. This restrains the quantity of possibly benefiting patients. Thirdly, albeit effortlessly monitored, immune reaction is administered against one or a couple of epitopes, conceivably diminishing the effectiveness of response and favoring mechanism of immune escape. At last, we ought to consider population andsubject specific variability in antigen preparing and presentation, which could influence the efficiency of such an approach.

DNA-based Vaccine

The standard of this methodology is based on the presumption that the DNA encoding for a given TAA can be taken by APCs, interpreted into protein, lastly handled for management[32]. DNA can be conveyed naked or complexed with different molecule. Often, the most utilized vectors are virus that have the capacity to proficiently transfect target cells.Recently, new innovations, for example, nanoparticles and liposome preparations have been effectively utilized to convey DNA vaccines. A substantial proof supports the thought that stimulating a coordinated immune response, including cellular, humoral, and innate immune effectors (NK cells and macrophages), most adequately intercedes tumor rejection[33-35]. DNA vaccines, due to their unique mechanism of action, could invigorate a more "physiologic" immune response against antigens and could be delivered on a bigger scale. Notwithstanding, discovering a viable vector can be challenging.

Dendritic cells-based vaccination

DCs are the most imperative APCs. They commonly express high amounts of MHC particles, co-stimulatory proteins, and cytokines. Autologous DCs can be altered by fusion with cancer cells by beating with peptides or by transfection to express tumor antigens. DC vaccinationrepresents a standout platforms in cancer vaccines. indeed, DCs have the capacity stimulate both class I and class II reactions and can be further changed keeping in mind the end goal to co-express molecule, and reactions can be directed against numerous targets[36]. This kind of platform has been effectively utilized and affirmed for clinical use in castration resistant prostate

cancer. However, this vaccine platform remains in fact challenging because of the instability identified with the ideal route of administration and development, maturation, andactivation of DC cells, which is not effortlessly achievable ex vivo and, therefore, this limits bigger scale production.

Whole cells-based vaccination

An alternate potential methodology is vaccinating the patient with entire tumor cells, inferred from the patient herself (autologous) or from cell-line culture (allogeneic). These vaccines have been indicated to affect antigen-specific T-cell reactions. On the other hand, tumor cells act as antigenic pool for in-vivo or ex-vivo APCs. To upgrade immunological reaction, tumor cells can be hereditarily altered to express co-stimulatory molecules or cytokines[37]. Theoretical advantages of such approach contain giving a pool of tumor antigens, producing immune reactions to more than one antigen, and in this way conceivably conquering the tumor antigen loss.Additionally, this could prompt a more "complex" reaction, including both CD4+ and CD8+ T-cells, against different antigens. Potential disadvantages may be the activating of autoimmunity and troubles in checking the subsequent immunologic reaction that may be guided against obscure TAAs[38].

Common mechanism prompting drug resistant to breast cancer

The three clinical sub types of breast cancer have different remedial methodologies, however the molecular mechanisms that offer climb to refractory disease have regular aspects, strikingly changes to the PIK3/Akt pathway, miRNA levels, and epigenetic modulation of gene transcription. These normal aspects will now be investigated together with their potential as target for adjuvant treatments to dodge drug resistance and restore clinical responsiveness[39].

PI3K/Akt pathway

The PI3K/Akt pathway is an essential signaling mechanism directing numerous cell reactions, including cell proliferation and survival in typical and also neoplastic breast tissue. It structures a meeting point between three clinical subtypes of Breast Cancer, and variations in this way happen in 70% of breast tumors independent of subtype.

As highlighted already, distortions in this pathway are imperative in resistance to both tamoxifen and trastuzumab, particularly as this pathway structures a crosslink between HER2 signaling and ERα-regulated gene transcription, and have likewise been connected to MDR1 up regulation and resistance to chemotherapeutics[40-41]. Therefore, understanding this pathway is making ready for new adjuvant medications in resistantBreast Cancer. Various changes can happen, yet all result in supported pathway movement. Common deviations incorporate activating transformations or intensification of any of the PI3K subunits p110α, p110β, or p85α or loss of PTEN action and its hindrance of PI3K, through inactivating mutations, over expression of miRNAs, or promoter hyper methylation. Both of these situations bring about expanded Akt phosphorylation and maintained Akt activation, the net impacts of which are restraint of apoptosis, transcription of ERα-dependent genes, and cell proliferation. A major downstream effector of Akt initiation that intercedes various reactions is mammalian target of rapamycin complex 1 (mTORC1)[42]. mTORC1 likewise act as a signaling integration hub accepting inputs from the MAPK pathways that may be disturbed in drug resistant breast cancer. Supported PI3K/Akt/mTORC1 movement might likewise be because of adjustments in miRNAexpression and can incite various epigenetic changes that sustain drug resistance.

MiRNA-intercededresistance

In the last decade it has become vibrant that alterations to MiRNA expression levels can contributecancer anticipation and outcome. miRNAs are little, noncoding RNAs andcontain 22 nucleotides, which bind to mRNA, avoiding translation and quickening mRNA de-adenylation and ensuing degradation, thus leading gene silencing effect. Several miRNAs have been connected with drug resistance in Breast cancer, and these focus on varieties of genes, including PTEN, ESR1 (ERα), FoxO3, and DNA (cytosine-5)-methyltransferases (DNMTs)[43].

The mechanism that prompt miRNAup regulation in drug resistantBreast cancer are at present vague, yet they have capable impacts. One miRNA that is overexpressed in both trastuzumab-resistant cells and cells impervious to chemotherapeutics is miR-21, which targets PTEN and results in supported PI3K/Akt pathway action. It additionally down regulates the apoptotic gene programmed cell death 4 (*PDCD4*), permitting cancer cells to avoid apoptosis. This protein is likewise inactivated by phosphorylation by S6K1, a downstream effector of the PI3K/Akt pathway[44]. Another noticeable miRNA that seems, by all accounts, to be imperative in drug resistance in both ERα- positive and triple-negative Breast cancer is miR-221, which target on the cell-cycle inhibitory protein p27Kip1, among others. Thus, it can be seen that miRNAs have critical role in intervening drug resistance in breast cancer. Though, the mechanism prompting miRNA overexpression are not yet completely understood.

Epigeneticregulation

There are three primary interlinked mechanisms by which epigenetic modulation prompts transcriptional

regulation, chromatin rebuilding, alteration of nucleosome synthesis, and change of epigenetic imprints, all of which have been ensnared in resistance to breast cancer treatments. ATP-dependent chromatin remodeling permits transcriptional complexes to access the profoundly coiled genomic DNA to start gene transcription[45]. This can be attained by selected transcription factor, known as pioneer components. One such family, the Fork heads (Fox), play vital role in breast cancer. Indeed, FoxA1 controls 50% of ERα target genes, and its expression, alongwith FoxP1, has been associated with tamoxifen treatment.Conversely, FoxM1 has a role to play in trastuzumab and paclitaxel resistance, as knockdown builds drug sensitivity in multidrug-resistant cell lines. FoxO1 expression is likewise connected with chemotherapeutic and tamoxifen resistance, as it manages the translation of both the MDR1 (P-gp) and ABCC2 (MRP2) drug efflux pumps.

The nuclear translocation of an alternate FoxO isoform, FoxO3a, is hindered by phosphorylation by Akt, which acts to drive cell multiplication and tamoxifen resistance, as FoxO3a has cytostatic activities by means of p27 up regulation and cell-cycle inhibition and by diminishing the interpretation of ERα-regulated genes. The science of this complex group of translation components is not completely understood, however it has become clear that the parity of expression of the distinctive isoforms is vital, and further studies are expected to completely portray their roles in drug resistant breast cancer[46].

Future outlook for the treatment of drug resistant breast cancer

The studies deliberated here portraying the molecular mechanismcausing drug resistance in breast tumor, regarding both single and multidrug resistance, have recognized various pathways that offer potential routes to evade resistance to the current treatments.

The PI3K/Akt/mTORC1 flagging offers target for therapeutic intercessions, and various clinical trials are progressing utilizing PI3K, AKT, mTOR, or double inhibitors in blend with endocrine or chemotherapies[47]. However, alert is needed, as the clinical response may rely upon particular abnormality and the subtype of Breast cancer, as restraint of Akt may prompt apoptosis by release of Bcl-2-associated death promoter (BAD) inhibition, however Akt restraint can likewise allow FoxO3a nuclear translocation, possibly prompting the translation of ERα-dependent gene empowering cell multiplication. Likewise, up regulation of growth factor receptors (e.g., FGFRs and IGF-1R) may support activation of other signaling cascades, for example, the MAPK pathways, which could be aggravated by hindrance of PI3K/Akt/mTORC1[48]. Likewise, the impacts of this pathway on translation through epigenetic changes need to be considered to keep the selection of tumor subpopulations that are impervious to treatment, particularly the FoxO family, as directing these transcription figures straightforwardly is not a reasonable optioncurrently, because of their complexity. Along these lines, the mix of treatments needs to be precisely considered and appropriate for the tumor subtype.

Closing Remarks:

The development of targeted treatments is an essential venture in the making of individualized cancer management. The conceivable target for treatments increase, in the meantime as our understanding of the mechanism underlying cancer progresses. Be that as it may, better understanding of which patients will gain most profit from targeted medications is still needed. Focus is presently on creating vigorous biomarkers keeping in mind the end goal to support expectation of reaction so that in future, patients will get only medications that will present leverage.

Recently, remarkable advancement has been accomplished around the cure of Breast Cancer. More customized treatments, molecularly targeted medications, and a deeper understanding of the mechanism of ailment have permitted enhancing the prognosis of specific subtypes of tumor. In this quickly changing situation, there is a growing enthusiasm for building up a powerful tumor vaccine. Tragically, none of the vaccine tried so far in clinical trials has ended up being "practice changing." Nevertheless, three imperative lessons can be drawn.

To start with, numerous vaccine evoke a measurable immunologic reaction, for example, particular antibodies or CD8+ T-cells, however this reaction has almost no effect on tumor development. Captivating one compartment of the immune framework (e.g., just cytotoxic reaction or humoral reaction) is most likely not sufficient for a successful therapeutic vaccine. New vaccination procedures ought to subsequently go for evoking a wide reaction, including various immune effectors, for example, cytotoxic and antibody secreting B-cells, innate immunity factors, and memory cells. The hidden idea would be that a "complete" immunological reaction may promote expanded release of tumor cell antigens and proinflammatory cytokines, bringing about an immunologic prudent cycle.

Secondly, the primary hindrance against vaccination is most likely because of complex immune escaping components created by tumor cells. Regulatory cells, for example, T-Regs and molecule immune checkpoints (e.g., CTLA-4, PD1/PD1L) play essential roles in keeping up self-tolerance toward oneself, and tumors have the capacity

to abuse these components to get protected from immune framework's assault. New procedures focused around blocking antibodies, recombinant manifestations of ligands, or receptors ought to be executed to block such modulatory checkpoints and reinforce the immune reaction, with promising initial interpretation into clinical setting. A standout amongst the most interesting points of view of these techniques is clearly their synergism with immunotherapy methodologies, for example, cancer vaccines.

Thirdly, subjects with extensive tumor load and last stage cancer, enrolled in a large portion of the clinical trials on cancer vaccine, are likewise those individuals who profit less from cancer vaccine alone. Indeed, as cancer advances and spreads despite different lines of treatment, immune resistance systems get to be more complex and the immune framework is less inclined to balance the tumor. Accordingly, in these patients, merging vaccine with FDA approved medications focusing on cancer biology, for example, endocrine treatment, tyrosine receptor inhibitors, or chemotherapy, is obliged to attain acceptable clinical results. Taking everything into account, to boost the probability of achievement, new Breast Cancervaccines ought to be created by incorporating an exhaustive understanding of immune resistance mechanisms and tried in decently planned clinical trials led in immunologically favorable settings. Besides, an extra exertion ought to be made to enhance immunotherapy in the particular basal-like subtype, which obliges novel remedial strategies more than luminal and HER2-positive types.

Conflicts of Interest Statement:

The Authors declare no conflicts of interest.

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